




RESEARCH PAPER



Effectiveness and failure rate of the varicella vaccine in an outbreak in Jiangsu, China: a 1:2 matched case-control study

Yong Wang ^a, Lei Zhang ^{a*}, Xiang Sun^{b*}, Yang Cao^{a*}, Zhiguo Wang^b, Li Liu^b, Yan Xu^b, Minghao Zhou ^{a,b}, and Yuanbao Liu^b

^aDepartment of Epidemiology, School of Public Health, Nanjing Medical University, Nanjing, Jiangsu Province, China; ^bDepartment of Expanded Programme on Immunization, Jiangsu Provincial Center for Disease Control and Prevention, Nanjing, Jiangsu Province, China

ABSTRACT

Background: The varicella vaccine is not included in the national childhood immunization schedules in China, although one-dose varicella vaccine has been suggested for susceptible children aged 1–12 years in Jiangsu Province. However, varicella epidemics and outbreaks are frequently reported. We investigated a varicella outbreak in an elementary school to explore the risk factors for varicella transmission and vaccine failure.

Methods: A 1:2 matched case-control study was carried out. Participant data were collected with standardized questionnaires. For each case, we enrolled two controls: a subject with high exposure in the same classroom as the case and a subject with low exposure in a different classroom. Data regarding vaccination status and medical and exposure histories were analyzed.

Results: Fifty-one cases were reported during the outbreak; 26 cases (51%) were breakthrough varicella. Varicella vaccine immunization history ($P < .001$, OR = 0.19, 95% CI = 0.08–0.45) and the presence of siblings ($P = .037$, OR = 0.45, 95% CI = 0.21–0.95) were protective factors in preventing varicella infection. Contact with varicella patients increased the risk of varicella infection ($P = .028$, OR = 3.39, 95% CI = 1.14–10.09). Breakthrough varicella cases tended to present a milder rash ($P = .049$), fewer complications ($P = .02$), fewer rash sites ($P = .02$) and a shorter duration of active lesions ($P = .001$). One pneumonia case and one encephalitis case were reported in breakthrough cases. Age <15 months at the time of vaccination increased the risk of breakthrough varicella ($P = .012$). The adjusted vaccine effectiveness was 81%.

Conclusions: One-dose varicella vaccine is effective at alleviating clinical manifestations. The moderate coverage provided by one dose cannot prevent varicella outbreaks, and vaccination after 15 months of age should be considered in the immunization schedule; a two-dose strategy is highly recommended.

ARTICLE HISTORY

Received 30 April 2019
Revised 26 August 2019
Accepted 3 September 2019

KEYWORDS

Varicella; vaccine; outbreak; effectiveness; vaccine failure

1. Introduction

Varicella is a highly contagious acute respiratory disease caused by a primary infection with the varicella zoster virus (VZV). It is characterized by systemic papules and pruritic varicella rashes, which are common in children and can lead to serious complications, such as pneumonia, encephalitis and even death¹. According to the China Information System for Disease Control and Prevention, in 2017, the incidence rate of reported varicella was over 40/100,000 population in Jiangsu, China, and varicella dominated all public health emergencies caused by infectious diseases. Varicella disease has become an increasingly serious issue for public health in China.

The live attenuated varicella vaccine (Oka strain) is now widely available globally and has been shown to be the most effective measure for the prevention and control of varicella.^{2–4} In China, the varicella vaccine was first licensed for use as a single dose in 1998 for children aged at least 12 months of ages.⁵ In some countries, such as the USA and Canada, varicella incidence and the following complications have been reduced by a routine childhood immunization programme.⁶ Although

the varicella vaccine is not included in the national childhood immunization schedules in China,⁷ the one-dose varicella vaccine has been suggested for children aged 1–12 years based on the guidelines for disease control. Although the coverage of the one-dose varicella vaccine has reached approximately 70%, 174 varicella outbreaks were reported in Jiangsu Province, China in 2018. Varicella is epidemic in Jiangsu, especially in children who received the one-dose varicella vaccine, and similar studies were limited. To explore the risk factors for varicella transmission and breakthrough cases, a 1:2 case-control study was conducted in an outbreak reported in a primary school in the southern region of Jiangsu Province, China.

2. Materials and methods

2.1. Outbreak setting

The outbreak took place in a public elementary school (School A) in the southern region of Jiangsu Province and involved first, second, fifth and sixth grade students. During the outbreak, 1461 students attended School A. The two three-story

CONTACT Minghao Zhou  zmhaocdc@sohu.com; Yuanbao Liu  lybaomc@163.com  Department of Epidemiology, School of Public Health, Nanjing Medical University, No.101, Longmian Avenue, Nanjing, Jiangsu Province, China

*These authors contributed equally to this study.

This article has been republished with minor changes. These changes do not impact the academic content of the article.

© 2019 Nanjing Medical University

school buildings (north and south) included 33 classrooms with five classrooms for Grade 1, five for grade 2, five for grade 3, six for grade 4, six for grade 5 and six for grade 6. The school has two “buildings” connected at the north and south ends respectively and grade 1 and grade 2 were on the first floor, grade 3 and grade 4 were on the second floor, and grade 5 and grade 6 were on the third floor. Students had contact with other students in other grades in the school canteen, hallways, playground, and school buses.

2.2. Study design

A 1:2 retrospective case-control study was initiated in June 2018 in Jiangsu Province, China. A case of varicella was defined as a pruritic maculopapular rash without another apparent cause that occurred from April 4 to May 19, 2018 in a student attending School A. Varicella and its complications were diagnosed by experienced doctors at the local hospital, who reported varicella in the National Disease Reporting System. The typical clinical manifestations for making a diagnosis are acute onset, and it may be accompanied with prodromal symptoms such as fever. The rash begins with red pimples, which then turn into vesicles within a few hours. As the herpes fluid becomes feculent, the vesicles rupture and ultimately scab. Breakthrough varicella was defined as a varicella-like rash that developed > 42 days after varicella vaccination. All cases were identified from the National Disease Reporting System. For each case, we enrolled two controls who had not had varicella: a subject with high exposure in the same classroom with the case and a subject with low exposure in a different classroom in the same grade.

The inclusion criteria for cases were as follows: (1) newly diagnosed clinical cases during this outbreak; (2) parents provided informed consent for the investigation; and (3) the children had complete medical information. The exclusion criteria for cases were as follows: (1) children had chronic dermatologic diseases including urticaria papulosa and pustular eruption that could interfere with the investigation. The inclusion criteria for controls were as follows: (1) children attended the same grade as the case; and (2) parents provided informed consent for the investigation. The exclusion criteria for controls were as follows: (1) children had a history of the disease; (2) children had an incomplete medical information.

2.3. Data collection

A questionnaire was completed through investigator interviews with the students' parents. The contents of the questionnaire included demographic information, varicella vaccination status, medical and exposure history and health habits. The questionnaire for the cases also included clinical manifestations, including the presence of fever, disease severity, rash sites, complications, and duration of active lesions. Our study protocol was submitted to the Jiangsu CDC Ethics Committee to receive a waiver. The varicella vaccination history of each student before the outbreak was obtained from the vaccination card or the Jiangsu Provincial Vaccine and Immunization Management System. The system records children's vaccination information provided by the nurses at the Vaccination Service Center (VSC), who

input information, including the type of vaccine, vaccination time, and vaccine manufacturer, when they vaccinate children. Rash severity was categorized as mild (<50 lesions), moderate (50–499 lesions), or severe (≥500 lesions). Severe complications include pneumonia, encephalitis, secondary bacterial infections, osteomyelitis, and sepsis¹.

2.4. Statistical analyses

Varicella vaccine coverage before the outbreak was calculated as the proportion of vaccinated students among the target students in the school. Varicella vaccine effectiveness (VE) was calculated as $(1-OR) \times 100\%$. Comparisons of categorical data were performed using the Pearson chi-square test or Fisher exact test. A conditional logistic regression analyses was used for the 1:2 case-control study to determine the factors leading to varicella infection and breakthrough varicella. Univariate regression variables with statistical significance were incorporated as adjustment variables into the multivariate regression model. The odds ratio (OR) with a 95% confidence interval (CI) was calculated. A p -value <0.05 was considered statistically significant. All statistical analyses were performed with R 3.5.0 software (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Outbreak

The outbreak lasted 45 days, from April 4 through May 19, 2018. There were 1461 students in School A, and the outbreak spread to grade 1, grade 2, grade 5 and grade 6, with no cases in grade 3 or grade 4. The inclusion steps are summarized in Figure 1. All of the cases were students. Among the 942 students in the study, 413 (43.8%) were female, and 601 (63.8%) had received the varicella vaccination before the outbreak. There were 51 cases in the outbreak; 35 (68.6%) were in grade 2, and 23 (45.1%) were female. The characteristics of students who were involved in the outbreak are summarized in Table 1. The varicella vaccine coverage percentages were 71.3%, 69.1%, 66.5%, 64.2%, 61.3% and 57.9% from grade 1 to grade 6, respectively. The overall attack rate was 5.5%, with 3.2%, 15.4%, 2.9%, and 0.5% in grades 1, 2, 5 and 6, respectively.

The index case was an 8-year-old boy from class 4 of grade 2 who was exposed to a neighborhood playmate with varicella; this boy had received a one-dose varicella vaccine before the outbreak. He had an onset of rash on April 1 and attended school the next day. With a generalized rash consisting of < 50 lesions, he was mildly ill and developed a headache. The outbreak was restricted to 9 classrooms in School A: 3 classrooms of grades 2 and 5, 2 classrooms of grade 1, and one of grade 6. Of the 51 cases, 26 had a history of varicella vaccination, and only one peak of cases ($n = 24$) was observed in this outbreak on April 15–16 (Figure 2).

3.2. Clinical features of the cases

Except for fever, significant differences were observed in rash severity, complications, number of rash sites, and duration of active lesions (see Table 2). In most of the vaccinated cases,

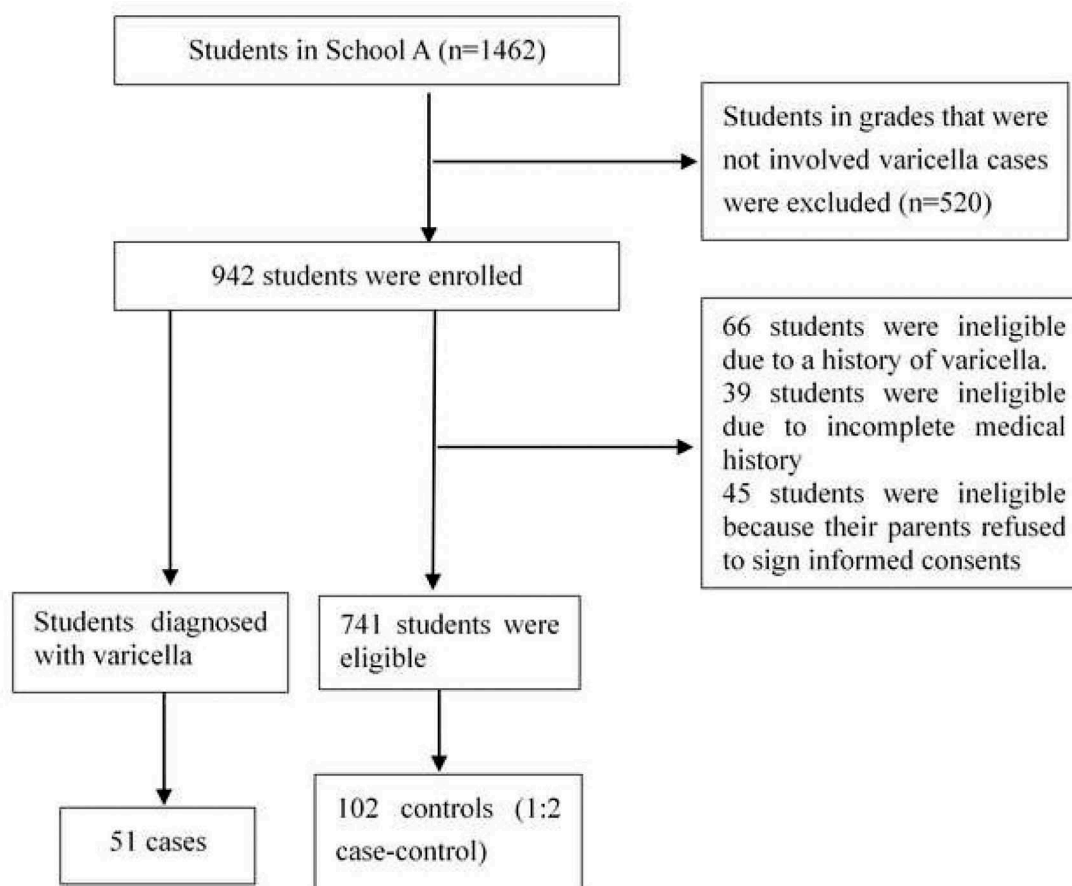


Figure 1. Inclusion steps for cases and controls.

Table 1. Characteristics of different grades involved in the outbreak in Jiangsu Province, China.

| | Grade 1 (N = 223) | Grade 2 (N = 228) | Grade 5 (N = 275) | Grade 6 (N = 216) |
|-------------------------|--------------------------|----------------------|----------------------|----------------------|
| Characteristic | Cases (AR ^a) | Cases (AR) | Cases (AR) | Cases (AR) |
| Ages (years) Median Sex | 7.3 | 8.3 | 11.1 | 12.4 |
| Female | 3 (1.4%) | 14 (6.2%) | 5 (1.8%) | 1 (0.5%) |
| Male | 4 (1.8%) | 21 (9.2%) | 3 (1.1%) | 0 (0.0%) |
| Susceptibility | | | | |
| History of varicella | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Unvaccinated | 3 (1.4%) | 16 (7.0%) | 5 (1.8%) | 1 (0.5%) |
| Vaccinated | 4 (1.8%) | 19 (8.4%) | 3 (1.1%) | 0 (0.0%) |
| Total | 7 (3.2%) | 35 (15.4%) | 8 (2.9%) | 1 (0.5%) |

^aAR: attack rate

rash severity was mild, the number of rash sites was fewer than 5, and the duration of active lesions was fewer than 10 days. Complications were reported in 3 vaccinated cases, including 1 with headache and 2 with vomiting, while 10 complications were reported in unvaccinated cases, including 4 with nausea, 3 with sore throat, 1 with vomiting, 1 with pneumonia, and 1 with encephalitis.

3.3. Vaccine effectiveness and risk factors leading to the varicella outbreak

Varicella vaccination was a protective factor against varicella transmission (crude OR = 0.25, adjusted OR = 0.19). The

crude VE was 75% (95% CI = 46%-89%), and the adjusted VE was 81% (95% CI = 55%-92%). Contact with varicella patients increased the risk of developing varicella (adjusted OR = 3.39, 95% CI = 1.14-10.09). The prevalence of siblings was a protective factor in the multivariate regression model (adjusted OR = 0.45, 95% CI = 0.21-0.95). Data are presented in Table 3.

3.4. Risk factors for vaccine failure

As Table 4 shows, vaccination at <15 months of age was more likely to be associated with vaccine failure ($P = .012$). The median interval between vaccination and the onset of the varicella rash in cases of breakthrough varicella was 81 (71-84) months. In addition, time since vaccination (≤ 5 years vs. >5 years) was not associated with varicella failure in this outbreak ($P = .505$) (see Figure 3).

4. Discussion

Through a 1:2 case-control survey, we investigated a varicella outbreak in a Jiangsu elementary school, where the one-dose varicella vaccine coverage was 64.5%, indicating that a moderate coverage of the one-dose varicella vaccine cannot interrupt the transmission of varicella.⁸⁻¹⁰ We also found milder disease in vaccinated cases compared to unvaccinated cases, and varicella vaccination and the presence of siblings

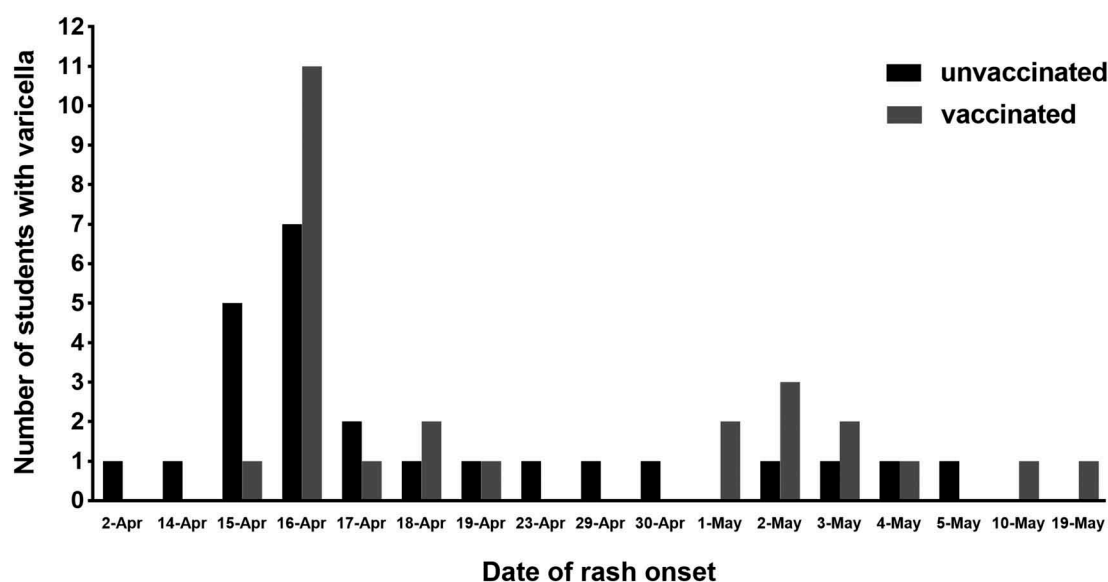


Figure 2. Varicella cases by date of rash onset and vaccination status.

Table 2. Comparisons of clinical features of vaccinated and unvaccinated cases.

| Clinical features | Vaccinated (N, %) | Unvaccinated (N, %) | χ^2 | P-value |
|------------------------------|-------------------|---------------------|----------|---------|
| Fever | | | 0.943 | 0.332 |
| Yes | 9 (34.6) | 12 (48) | | |
| No | 17 (65.4) | 13 (52) | | |
| Rash severity | | | 5.453 | 0.049* |
| Mild (<50 lesions) | 23 (88.5) | 15 (60) | | |
| Moderate (50–499 lesions) | 3 (11.5) | 8 (32) | | |
| Severe (≥ 500 lesions) | 0 (0.0) | 2 (8) | | |
| Complications | | | 5.436 | 0.02 |
| Yes | 3 (11.5) | 10 (40) | | |
| No | 23 (88.5) | 15 (60) | | |
| Number of rash sites | | | 7.783 | 0.02 |
| 1–2 | 7 (26.9) | 8 (32) | | |
| 3–4 | 12 (46.2) | 3 (12) | | |
| ≥ 5 | 7 (26.9) | 14 (56) | | |
| Duration of active lesions | | | 10.702 | 0.001 |
| ≤ 10 days | 17 (65.4) | 5 (20) | | |
| > 10 days | 9 (34.6) | 20 (80) | | |

*Fisher's exact test.

were protective factors that prevented varicella infection, while age <15 months at the time of vaccination increased the risk of breakthrough varicella. All these findings add new evidence supporting the introduction of the two-dose varicella vaccine in children older than 15 months. In addition, this study provides important guidance for the prevention and control of varicella in Jiangsu Province. Although studying in the same school and sharing the canteen, playground and transport, no students in grades 3 and 4 suffered from varicella. Grades 3 and 4 were on a different floor than the other grades, and therefore, students of those grades were less likely to be exposed to the VZV virus. Students were immediately isolated after being diagnosed with varicella, and all collective activities were canceled. This may suggest that infection was mainly due to the presence of the VZV virus in the teaching area. Although the one-dose varicella vaccine provided insufficient protection against breakthrough cases,^{11–14} the clinical manifestations of breakthrough varicella tended to be mild or moderate. The results of this study showed that the one-dose varicella vaccination was highly effective in alleviating the

clinical manifestations. Additionally, breakthrough cases had a shorter duration of active lesions and fewer rash sites, as shown in previous published studies.^{3,15,16} Serious complications, such as pneumonia and encephalitis, occurred in unvaccinated students.

The adjusted ORs showed that the presence of siblings, contact with varicella patients and having received the one-dose varicella vaccine were associated with the varicella outbreak. As previous findings have shown, contact, especially with those exposed to varicella cases in schools, can effectively transmit varicella in a very short time due to the high contact rate among students.^{2,17} Students who had contact with varicella patients were 3.39 times more likely to contract varicella than those who did not. While a case-control study demonstrated that the children living in the same room with other children had a higher risk of varicella infection compared to those living alone,² this study indicated that the presence of siblings reduced the risk of varicella infection and was a protective factor. We found that most of the subjects' siblings also had been vaccinated with the varicella vaccine, which implied that a moderate level of coverage can partly interrupt the transmission of varicella, especially in one family. This is consistent with other reports that children with siblings had a higher proportion of VZV antibody seroprevalence.^{18,19}

The adjusted VE (81%) was similar to that calculated in a meta-analysis of 42 studies on the varicella vaccine²⁰ and clearly showed that the one-dose varicella vaccination was effective at preventing varicella infection. The WHO has suggested that vaccine coverage should be maintained at $\geq 80\%$, and for a one dose strategy, a coverage level $>85\%$ has been suggested in Australia. Nevertheless, the one-dose varicella vaccine strategy, regardless of whether the coverage was low, high or moderate, has not prevented outbreaks in China.^{10,21,22} The age at initial varicella vaccination was identified as a factor for vaccine failure in this study, as we found that children who received the first varicella vaccine at < 15 months of age had

Table 3. Risk factors for varicella infection in the outbreak, Jiangsu Province, China.

| Variable | Cases n (%) | Controls n (%) | P-value | Crude OR (OR95% CI) | P-value* | Adjusted OR * (OR 95% CI) |
|---------------------------------|-------------|----------------|---------|---------------------|----------|---------------------------|
| Age (years) X ± s | 8.7 ± 1.4 | 8.7 ± 1.1 | 0.563 | 0.16(0.86–1.32) | 0.512 | 1.04(0.84–1.36) |
| Sex | | | | | | |
| Female | 23 (45.1) | 43 (42.2) | 0.787 | 1.09 (0.58–2.06) | 0.276 | 1.50 (0.72–3.13) |
| Male | 28 (54.9) | 59 (47.8) | | 1 | | 1 |
| Presence of siblings | | | | | | |
| Yes | 20 (39.2) | 56 (54.9) | 0.081 | 0.56 (0.29–1.08) | 0.037 | 0.45 (0.21–0.95) |
| No | 31 (60.8) | 46 (45.1) | | 1 | | 1 |
| Region | | | | | | |
| Locals | 22 (43.1) | 41 (67.2) | 0.776 | 1.08 (0.62–1.89) | 0.663 | 0.82 (0.34–1.99) |
| Outsiders | 29 (56.9) | 61 (32.8) | | 1 | | 1 |
| Contact with varicella patients | | | | | | |
| Yes | 42 (82.3) | 69 (67.6) | 0.071 | 2.38 (0.93–6.11) | 0.028 | 3.39 (1.14–10.09) |
| No | 9 (17.7) | 33 (32.4) | | 1 | | 1 |
| Transportation to school | | | | | | |
| Private car | 14 (27.5) | 20 (19.6) | 0.247 | 1.46 (0.77–2.74) | 0.136 | 2.14 (0.79–5.84) |
| School bus | 7 (13.7) | 6 (8.8) | 0.125 | 1.90 (0.84–4.33) | 0.265 | 2.12 (0.57–7.91) |
| Walking | 30 (58.8) | 76 (71.6) | | 1 | | 1 |
| Frequency of hand washing | | | | | | |
| Frequently | 8 (15.7) | 18 (17.6) | 0.427 | 0.58 (0.15–2.23) | 0.907 | 0.91 (0.19–4.24) |
| Sometimes | 30 (58.8) | 64 (62.7) | 0.347 | 0.69 (0.28–1.58) | 0.333 | 0.61 (0.22–1.67) |
| Seldom | 13 (25.5) | 20 (19.7) | | 1 | | 1 |
| Vaccination status | | | | | | |
| One-dose | 26 (51) | 83 (81.4) | <0.001 | 0.25 (0.11–0.5) | <0.001 | 0.19 (0.08–0.45) |
| Unvaccinated | 25 (49) | 19 (18.6) | | 1 | | 1 |

*Adjusted for the presence of siblings, contact with varicella patients and vaccination status.

Table 4. Potential risk factors for varicella failure.

| Variable | Vaccinated students with varicella (n, %) | Vaccinated students without varicella (n, %) | P value* |
|---|---|--|----------|
| Age (years) Median (quartile) | 8.17 (6.5–11.5) | 8.29 (6.8–11.9) | 0.841 |
| Sex | | | 0.572 |
| Males | 12 (46.2) | 28 (53.8) | |
| Females | 14 (53.8) | 24 (46.2) | |
| Age at vaccination < 15 months | 15 (56.7) | 14 (26.9) | 0.012 |
| ≥ 15 months | 11 (43.3) | 38 (73.1) | |
| Time since vaccination before outbreak | | | 0.505 |
| ≤ 5 years | 5 (19.2) | 7 (13.5) | |
| >5 years | 21 (80.8) | 45 (86.5) | |

*Conditional logistic regression analysis.

a significantly higher risk of developing a breakthrough case in the following 2–5 years. The potential mechanism may be related to the immature immune system in younger children compared to the immune system in those older than 15 months.^{4,8,23} Study showed that maternal antibodies have a negative impact on infant antibody responses in an epitope-specific and titer-specific manner.²⁴ This suggests that transplacentally acquired maternal anti-varicella Abs may reduce the vaccine effectiveness in younger children. The estimated duration of protection against varicella by maternal antibodies among infants in the general population is 3.4 months.²⁵ Previous investigations demonstrated that time since vaccination, such as five years, could be a risk factor for breakthrough varicella.^{26–29} This suggests that immunity wanes with time; the initial response to the varicella vaccination is attenuated and the effectiveness over time is reduced for a one-dose vaccine. However, another case-control study showed that the vaccine provided stable levels of protection during the 2–8 years after vaccination.³⁰ In our study, time since vaccination was not associated with an increased risk of vaccine failure. As Figure 3 shows, it seems that there was a similar tendency of

the interval between vaccination and infection for vaccinated cases compared to vaccinated cases without varicella.

There are limitations in this study. First, as a case-control study, although selection targets had strict inclusion and exclusion criteria, selection bias was still difficult to avoid. The chronological order of exposure and disease was usually difficult to judge. Second, some data, such as exposure history and number of rash sites, were collected according to parent recall, and there may be recall bias.

In summary, a single-dose varicella vaccine is highly effective at preventing varicella infection but cannot interrupt outbreaks in school settings in Jiangsu Province, China. This study demonstrated that in settings with moderate varicella vaccine coverage, contact history was a risk factor, and the presence of siblings may be a protective factor in varicella outbreaks. A two-dose varicella vaccine schedule should be recommended for children before primary school, and vaccination after 15 months of age should be considered in the immunization schedule.

Acknowledgments

We greatly appreciate the help we received from the Jiangsu Center for Disease Control and Prevention (CDC), the Changzhou CDC and the Wujin CDC. We also thank the school staff for their assistance with the investigation.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

Funding

This work was supported by the “333” Project of Jiangsu Province, grant number BRA2017538, and the Preventive Medicine Association of Jiangsu Provincial Health and Family Planning Commission, grant number Y2017072.

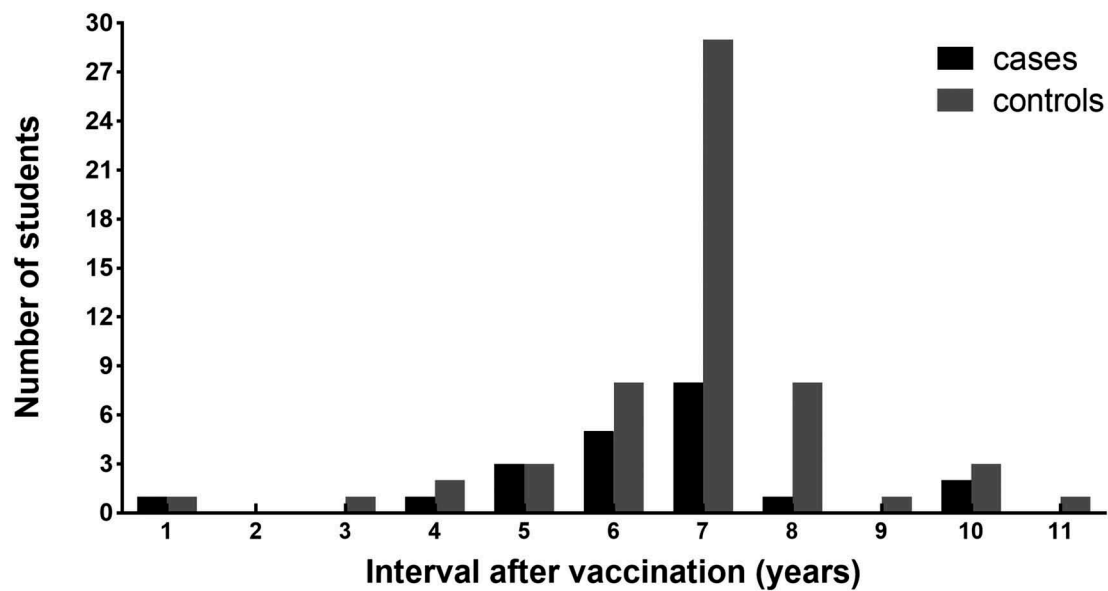


Figure 3. Breakthrough cases and vaccinated controls by interval after vaccination.

ORCID

Yong Wang <http://orcid.org/0000-0001-6573-1726>
 Lei Zhang <http://orcid.org/0000-0002-0083-6583>
 Minghao Zhou <http://orcid.org/0000-0003-1504-3591>

References

- Gershon AA. Is chickenpox so bad, what do we know about immunity to varicella zoster virus, and what does it tell us about the future? *Journal of Infection*. 2017;74:S27–S33. doi:10.1016/S0163-4453(17)30188-3.
- Andrade AL, Da Silva Vieira MA, Minamisava R, Toscano CM, de Lima Souza MB, Fiaccadori F, Figueiredo CA, Curti SP, Nerger MLBR, Bierrenbach AL. Single-dose varicella vaccine effectiveness in Brazil: A case-control study. *Vaccine*. 2018;36:479–83. doi:10.1016/j.vaccine.2017.12.011.
- Thomas CA, Shwe T, Bixler D, Del Rosario M, Grytdal S, Wang C, Haddy LE, Bialek SR. Two-dose varicella vaccine effectiveness and rash severity in outbreaks of varicella among public school students. *Pediatr Infect Dis J*. 2014;33:1164–68. doi:10.1097/INF.0000000000000444.
- Wang Z, Yang H, Li K, Zhang A, Feng Z, Seward JF, Bialek SR, Wang C. Single-dose varicella vaccine effectiveness in school settings in China. *Vaccine*. 2013;31:3834–38. doi:10.1016/j.vaccine.2013.06.075.
- Suo L, Lu L, Wang Q, Yang F, Wang X, Pang X, Marin M, Wang C. Varicella outbreak in a highly-vaccinated school population in Beijing, China during the voluntary two-dose era. *Vaccine*. 2017;35:4368–73. doi:10.1016/j.vaccine.2017.06.065.
- Heininger U, Seward JF. Varicella. *Lancet*. 2006;368:1365–76. doi:10.1016/S0140-6736(06)69561-5.
- Qi Y, Zhu Z, Shi Z, Ge Y, Zhao K, Zhou M, Cui L. Dysregulated microRNA Expression in Serum of Non-Vaccinated Children with Varicella. *Viruses*. 2014;6:1823–36. doi:10.3390/v6041823.
- Galil K, Lee B, Strine T, Carraher C, Banghman AL, Eaton M, Montero J, Seward J. Outbreak of varicella at a day-care center despite vaccine. *N Engl J Med*. 2002 Dec 12;347(24):1909–15. doi:10.1056/NEJMoa021662.
- Civen R, Lopez AS, Zhang J, Garcia-Herrera J, Schmid DS, Chaves SS, Mascola L. Varicella outbreak epidemiology in an active surveillance site, 1995–2005. *J Infect Dis*. 2008;197(Suppl 2):S114–9. doi:10.1086/522144.
- Parker AA, Reynolds MA, Leung J, Anderson M, Rey A, Ortega-Sanchez IR, Schmid DS, Guris D, Gensheimer KF. Challenges to implementing second-dose varicella vaccination during an outbreak in the absence of a routine 2-dose vaccination requirement—Maine, 2006. *J Infect Dis*. 2008; 197 (Suppl 2):S101–7.
- Lu L, Suo L, Li J, Zhai L, Zheng Q, Pang X, Bialek SR, Wang C. A varicella outbreak in a school with high one-dose vaccination coverage, Beijing, China. *Vaccine*. 2012;30:5094–98. doi:10.1016/j.vaccine.2012.05.072.
- Fu C, Wang M, Liang J, Xu J, Wang C, Bialek S. The effectiveness of varicella vaccine in China. *Pediatr Infect Dis J*. 2010;29:690–93. doi:10.1097/INF.0b013e3181d7380e.
- Shapiro ED, Vazquez M, Esposito D, Holabird N, Steinberg SP, Dziura J, LaRussa PS, Gershon AA. Effectiveness of 2 doses of varicella vaccine in children. *J Infect Dis*. 2011;203:312–15. doi:10.1093/infdis/jiq052.
- Lai CC, Chen SC, Jiang DD. An outbreak of varicella among schoolchildren in Taipei. *BMC Public Health*. 2011;11:226. doi:10.1186/1471-2458-11-226.
- Wu QS, Liu JY, Wang X, Chen YF, Zhou Q, Wu AQ, Wang L. Effectiveness of varicella vaccine as post-exposure prophylaxis during a varicella outbreak in Shanghai, China. *Int J Infect Dis*. 2018;66:51–55. doi:10.1016/j.ijid.2017.10.016.
- Lee B, Feaver S, Miller C, Hedberg C, Ehresmann K. An elementary school outbreak of varicella attributed to vaccine failure: policy implications. *J Infect Dis*. 2004;190:477–83. doi:10.1086/422041.
- Zhang X, Yan Y, Liu F, Luo Y, Zhang J, Peng X, Zhang Y, Han S, Zhao J, He Y. The epidemiology and risk factors for breakthrough varicella in Beijing Fengtai district. *Vaccine*. 2012;30:6186–89. doi:10.1016/j.vaccine.2012.07.062.
- Majidy P, Khodabandehloo M, Azadi NA. Seroprevalence of varicella zoster virus antibody among young women before marriage in Sanandaj, Iran. *Iran J Microbiol*. 2016;8: 147–52.
- Wiese-Posselt M, Siedler A, Mankertz A, Sauerbrei A, Hengel H, Wichmann O, Poethko-Müller C. Varicella-zoster virus seroprevalence in children and adolescents in the pre-varicella vaccine era, Germany. *BMC Infect Dis*. 2017;17:356. doi:10.1186/s12879-017-2461-2.
- Marin M, Marti M, Kambhampati A, Jeram S, Seward J. Global varicella vaccine effectiveness: a meta-analysis. *Pediatrics*. 2016;137:e20153741. doi:10.1542/peds.2015-3741.

21. Zhu YF, Li YF, Du Y, Zeng M. Epidemiological characteristics of breakthrough varicella infection during varicella outbreaks in Shanghai, 2008–2014. *Epidemiol Infect.* 2017;145:2129–36. doi:10.1017/S0950268817000772.
22. Fu J, Wang J, Jiang C, Shi R, Ma T. Outbreak of varicella in a highly vaccinated preschool population. *Int J Infect Dis.* 2015;37:14–18. doi:10.1016/j.ijid.2015.06.003.
23. Verstraeten T, Jumaan A, Mullooly J, Seward J, Izurieta H, DeStefano F, Black SB, Chen RT. A retrospective cohort study of the association of varicella vaccine failure with asthma, steroid use, age at vaccination, and measles-mumps-rubella vaccination. *Pediatrics.* 2003;112:e98–103. doi:10.1542/peds.112.2.e98.
24. Siegrist CA. Mechanisms by which maternal antibodies influence infant vaccine responses: review of hypotheses and definition of main determinants. *Vaccine.* 2003;21:3406–12. doi:10.1016/s0264-410x(03)00342-6.
25. Waaijenborg S, Hahne SJ, Mollema L, Smits GP, Berbers GA, van der Klis FR, de Melker HE, Wallinga J. Waning of maternal antibodies against measles, mumps, rubella, and varicella in communities with contrasting vaccination coverage. *J Infect Dis.* 2013;208:10–16. doi:10.1093/infdis/jit143.
26. Tugwell B, Lee L, Gillette H, Lorber E, Hedberg K, Cieslak P. Chickenpox outbreak in a highly vaccinated school population. *Pediatrics.* 2004;113:455–59. doi:10.1542/peds.113.3.455.
27. Haddad M, Hill M, Pavia A, Green C, Jumaan A, De A, Rolfs RT. Vaccine effectiveness during a varicella outbreak among schoolchildren: utah, 2002–2003. *Pediatrics.* 2005;115:1488–93. doi:10.1542/peds.2004-1826.
28. Kurugol Z, Halicioglu O, Koc F, Koturoglu G, Aksit S. Varicella rates among unvaccinated and one-dose vaccinated healthy children in Izmir, Turkey. *Int J Infect Dis.* 2011;15:e475–80. doi:10.1016/j.ijid.2011.03.016.
29. Chaves S, Gargiullo P, Zhang J, Civen R, Guris D, Mascola L, Seward JF. Loss of vaccine-induced immunity to varicella over time. *N Engl J Med.* 2007;356:1121–29. doi:10.1056/NEJMoa064040.
30. Vázquez M, LaRussa P, Gershon A, Niccolai L, Muehlenbein C, Steinberg S, Shapiro ED. Effectiveness over time of varicella vaccine. *JAMA.* 2004;291:851–55. doi:10.1001/jama.291.7.851.